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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
RAO, DEEPAK R

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/717,051	SOUTH ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,17-24,38 and 40-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,17-24,38 and 40-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on December 13, 2004.

Claims 1-2, 17-24, 38 and 40-49 are pending in this application.

Response to Amendment

The amendment to the claims filed on December 13, 2004 does not comply with the requirements of 37 CFR 1.121(c) because claim 49 was not present prior to the filing of the amendment and the status of the claim is indicated as "currently amended". Also, the listing of the claims indicates that "claim 50 is cancelled", however, claim 50 was not present in the application. Only claims 1-48 were present in the application as indicated in the previous office action(s). The record does not show that claims 49 and 50 were present in the application prior to the filing of the current amendment. In the listing of the claims, claim 49 should have been identified as "(New)" and claim 50 should not have been present.

Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. **In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression**: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), **(New)**, and (Not entered).

(1) *Claim listing.* All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (*e.g.*, Claims 1–5 (canceled)). The claim listing

shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

(2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

(3) *When claim text in clean version is required.* The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, *i.e.*, without any markings in the presentation of text. The presentation of a clean version of any claim having the status of "original," "withdrawn" or "previously presented" will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of "withdrawn" or "previously presented." Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

(4) *When claim text shall not be presented; canceling a claim.*

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered."

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim.

(5) *Reinstatement of previously canceled claim.* A claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained and/or necessitated by the amendments:

1. Claims 38 and 40-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating thrombosis, does not reasonably provide enablement for (a) inhibiting (i) thrombotic conditions and (ii) thrombus formation in blood; and (b) treating and/or preventing the conditions recited in claims 43-48. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference. Additionally, the following reasons are provided.

The use disclosed in the specification is as anticoagulants for the treatment of thrombotic diseases requiring anticoagulant therapy. The specification provides that the compounds of the invention are capable of inhibiting activity of serine proteases related to the coagulation cascade, however, there are no test assays or data provided to demonstrate the activity of the compounds. Test data is provided on pages 209-210, however, there is no disclosure regarding how this data correlates with 'inhibiting thrombotic conditions' in general or 'treating or preventing' of various diseases of the instant claims. The data range provided for the compounds is insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the myriad of compounds embraced by the structural formula of the claims. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to factor Xa inhibitors or anticoagulants) for assuming the same. The area of receptor interactions is highly structure

specific and unpredictable. The direction and extent of effects of anticoagulant interactions are not completely predictable. Furthermore, the results of the biological tests appear to be highly structure specific based on the range provided for the measured examples. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP э 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art.

The state of the art is not indicative of any anticoagulant agents for inhibiting thrombotic conditions in general. Further there are no known therapeutic or preventative agents for thrombotic conditions generally. Majerus et al. (cited in IDS) regarding Primary Prevention of Arterial Thromboembolism states that "the prophylactic use of aspirin in an apparently healthy population is not recommended at this time, unless there are risk factors for cardiovascular disease" (see page 1357). This clearly establishes that many factors need to be evaluated prior to administering anticoagulant or antiplatelet drug therapy in normal individuals. The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant preventive method. Prevention is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that symptoms of thrombotic conditions such as coronary artery diseases, cerebrovascular diseases, etc. never manifest themselves. The state of the art reference, Handin (cited in IDS), states that "There are no clinical tests to screen patients suspected of having hypercoagulable or prethrombotic disorders", thereby indicating the difficulty in identifying the 'patients in need of' the preventive treatment. The data and evidence provided in the instant

disclosure leads the examiner to doubt the objective truth of assertions of prevention of the thrombotic conditions of the claims. Venous thromboembolism is often clinically silent. As a result, studies evaluating the efficacy of preventive measures generally screen patients who are asymptomatic. As widespread screening is not recommended in general practice, the incidence of venous thromboembolism in most studies appears higher than that encountered in clinical practice. The importance of clinically undetected venous thromboembolism is not fully understood. Also, the diagnosis of pulmonary embolism with or without pulmonary infarction is often difficult to establish unless special procedures are used.

Further, the scope of the method claims recites not only treatment but also "prevention" which is not adequately enabled solely based on the activity related to thrombin inhibition or anticoagulation provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. Based on the IC_{50} data (see specification page 210), the instant compounds are disclosed to be useful in the "prevention" of diseases such as venous thromboembolism, pulmonary embolism, etc., for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. The specification provides IC_{50} values for the exemplified compound, however, it is inconceivable from this data as to how the claimed compounds can not only treat but also "prevent" a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being

reasonably predictive of success in any of the contemplated areas of "prevention". Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). The evidence presented in this case does not show such utilities related to "prevention", but only warrants further study.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rauch et al., (article enclosed) wherein with regards to antithrombotic therapies, it is stated that, "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al., (article enclosed) with regards to therapeutic approach of thromboembolic disorders, expresses that 'thrombin inhibitors have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'.

A patient's risk of venous thromboembolism varies depending on multiple factors including age, medical condition, type of surgery, duration of immobilization, and the presence of an underlying hypercoagulable state such as malignancy. Also, the site of cardiogenic thromboembolism is variable. Thromboembolism uncommonly occurs in the setting of a

structurally normal or mildly abnormal heart. Effective recommendations for prevention of arterial thromboembolism have not been identified. Therefore, primary prevention of thromboembolism is basically a battle against the underlying cardiac disorder. No therapies have been identified that reverse or significantly retard the development of feline heart disease or its related pathologic or prothrombotic sequelae. Moreover, it is likely that multiple interactions are involved in thrombogenesis, including myocardial pathology and cardiac dysfunction, platelets, and other blood components and factors. Furthermore, there is no evidence of record which would enable the skilled artisan in the identification of the subjects that have the potential of needing such 'prevention of the diseases' encompassed by the instant claims. Regarding prevention of stroke, a state of the art reference, Hart et al. (article enclosed), states that "Critical issues involving prevention of stroke for millions of persons with atrial fibrillation remain to be resolved by the next generation of studies. Reliable schemes to predict stroke risk must be refined and validated, and optimal antithrombotic prophylaxis awaits better understanding of the mechanisms linking predictors to stroke."

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in preventing diseases that require thrombin inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the pharmacokinetics and anticoagulant effects of thrombin inhibitors are unpredictable.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the >preventive= effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, Athe scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved≅. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: The specification discloses that >the dosage regimen is selected depending on a variety of factors= (see page 20, lines 20-26), however, the state of the art is that the effects of thrombin inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace not only treatment but also the **prevention** of diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples

regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed methods.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards "preventing" the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'it is not necessary that the specification disclose an exact correlation between the in vitro data regarding the inhibition of certain coagulation factors and in vivo results relating to the inhibition of thrombosis generally'. However, it was clearly indicated in the previous office action the unpredictability of therapeutic approach related to many of the diseases encompassed by the instant claims and applicant did not provide any explanation as to how treatment or prevention of all types of thrombotic diseases of the claims is enabled. Further, one skilled in the art recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to various disease states, making it even more challenging to have a single therapeutic agent for the treatment of diverse thrombotic diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule for treatment of any particular disease. A

detailed understanding of the molecular mode of action of the thrombosis or coagulation factors alongside the elucidation of the molecular pathology of individual disease is required to identify the disease symptoms and individual patients that may benefit most from treatment or prevention. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters for each individual disease therapeutic intervention.

2. Claims 1, 2, 17-24, 38 and 40-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 17-24 and 38-39 of copending Application No. 10/215,292 (corresponding Publication No. 2003/0023086). The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments based on MPEP 804(I)(B) have been fully considered. The MPEP provides that "The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application, unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent." As the provisional double patenting rejection is not the only rejection pending in this application, it is maintained in the absence of arguments to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 21, 2005

Deepak Rao
Primary Examiner
Art Unit 1624